【Title】

Extra-hepatic Feeding Arteries of Hepatocellular Carcinoma: An Investigation Based on Intra-Arterial CT Aortography Images using an Angio-MDCT System.

【Author names and affiliations】

Ken Takada [a, d, *], Takanori Ito [b], Takashi Kumada [b], Hidenori Toyoda [b], Toshifumi Tada [b], Yasuhiro Sone [c], Tokio Endo [a], Keisuke Tanaka [a], Hirofumi Kitagawa [a], Katsuhiro Ichikawa [e]

[a] Department of Medical Technology, Ogaki Municipal Hospital, Ogaki, Japan

[b] Department of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Ogaki, Japan

[c] Department of Radiology, Ogaki Municipal Hospital, Ogaki, Japan

[d] Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan

[e] Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan

* Corresponding author

Email: takada121@gmail.com

Tel: +81 584 81 3341

Fax: +81 584 75 5715

Title

Extra-hepatic Feeding Arteries of Hepatocellular Carcinoma: An Investigation Based on Intra-Arterial CT Aortography Images using an Angio-MDCT System.

Abstract

Objectives: We investigated the frequencies and factors associated with the presence of extra-hepatic feeding arteries (EHFAs) of hepatocellular carcinoma (HCC) using intra-arterial CT aortography images.

Methods: A total of 173 patients with HCC who underwent transarterial chemoembolization (TACE) in our institution between January 2013 and March 2015 were enrolled. The types of EHFAs were evaluated by CT aortography images using an apparatus that combines multidetector-row computed tomography and angiography system. In addition, factors associated with the presence of EHFAs were determined.

Results: EHFAs were present in 22 (12.7%) patients with HCC. EHFAs most frequently branched from the right inferior phrenic artery (n=19), while others branched from the right adrenal artery (n=2), right renal artery (n=2), right internal thoracic artery (n=2), branches of the superior mesenteric artery (n=1), and an unknown artery from the aorta (n=1). Factors significantly associated with the presence of EHFAs in multivariate

analysis were tumor size ≥ 30 mm (hazard ratio (HR), 5.233 [95% confidence interval (CI), 1.507–17.413]; p = 0.009) and number of prior TACE treatments ≥ 3 (HR, 6.847 [95% CI, 1.928–24.311]; p = 0.003).

Conclusions: EHFAs of HCC were assessed with CT aortography images. Repeat TACE treatments and large tumor size were risk factors for the presence of EHFAs.

Highlights

- Multi detector-raw computed tomography angiography can assess extrahepatic feeding of hepatocellular carcinoma entirely.
- Multi detector-raw computed tomography can assessed extrahepatic feeding of hepatocellular carcinoma difficult to find by angiography.
- Factors significantly associated with the presence of EHFAs in multivariate analysis were tumor size ≥ 30 mm and number of prior transarterial chemoembolization treatments ≥ 3.

Keywords

Hepatocellular carcinoma (HCC); extra-hepatic feeding arteries; transarterial chemoembolization (TACE); angiography; multi detector-row computed tomography

(MDCT)

Abbreviations:

TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma; EHCAs, extra-hepatic collateral feeding arteries; MDCT, multidetector-row computed tomography; angio-MDCT, apparatus that combines multidetector-row computed tomography and angiography system; 3D, 3-dimensional; HR, hazard ratio; CI, confidence interval; DSA, digital subtraction angiography; CT, computed tomography; CTHA, computed tomography during hepatic arteriography; CTAo, computed tomography during aortography; HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, α-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive α-fetoprotein, DCP; des-γ-carboxy prothrombin; EASL, European Association For The Study Of The Liver; US, ultrasonography; MRI, magnetic resonance imaging; ROC, receiver operating characteristic curve; LAT, locoregional ablative therapy; HAIC, hepatic arterial infusion chemotherapy; RIPA, right inferior phrenic artery; RARA, right adrenal artery; SMA, superior mesenteric artery; RRA, right renal artery; ITA, internal thoracic artery.

Introduction

Hepatocellular carcinoma (HCC) is currently the third and fifth most common cause of cancer-related deaths in men and women in Japan, respectively [1]. Transcatheter arterial chemoembolization (TACE) is a mainstay of treatment for unresectable HCC, especially in the intermediate stage [2, 3]. In addition, it has been reported that TACE improves survival rates in HCC patients [4, 5].

Extra-hepatic feeding arteries (EHFAs) sometimes contribute to the blood supply of HCC and complicate the TACE procedure. Failure to detect EHFAs reduce treatment efficacy. It is therefore important to have sufficient knowledge regarding EHFAs in HCC patients, and to assess these collateral pathways while performing TACE.

Previous studies have almost always evaluated EHFAs of HCC using selective angiography [6, 7], but this method is not sufficiently sensitive. We recently reported the utility of a newly developed apparatus that combines multidetector-row computed tomography (MDCT) and an angiography system (angio-MDCT) [8]. It is possible to perform intra-arterial CT aortography (CTAo) using angio-MDCT, and the images obtained by CTAo include comprehensive information on all arteries in the scan range. Therefore, in contrast to the conventional method, CTAo allows us to evaluate all EHFAs that are present.

The aim of the present study was to investigate the frequencies and factors associated with the presence of EHFAs in HCC patients using intra-arterial CTAo images derived with the angio-MDCT system.

Materials and methods

Patient selection and analysis

Between January 2013 and March 2015, a total of 302 patients with HCC underwent TACE using the angio-MDCT system at the Department of Gastroenterology of Ogaki Municipal Hospital, Japan. When individuals underwent more than one TACE procedure during this period, we used patient data at the first time of TACE. Therefore, 173 HCC patients were eventually included in this study.

The diagnosis of HCC was confirmed based on the European Association for the Study of The Liver (EASL) guidelines [9]. All laboratory data were measured at the time of HCC diagnosis, including blood tests for tumor markers of HCC (α-fetoprotein [AFP], *Lens culinaris* agglutinin-reactive α-fetoprotein [AFP-L3], and des-γ-carboxy prothrombin [DCP]). The study protocol was approved by the institutional review board of Ogaki Municipal Hospital and conducted in compliance with the Helsinki Declaration.

Construction of 3-dimensional vascular images using CT aortography protocol

An angio-MDCT system consisting of 64-MDCT (Aquilion CX; Toshiba Medical Systems) and angiography units with digital subtraction angiography (DSA) equipment and a C-arm (Infinix Celeve-I INFX 8000C; Toshiba Medical Systems) was introduced at our institution in December 2012. All CT images in the present study were obtained using this system.

The entire treatment procedure was performed under local anesthesia with lidocaine. After the placement of a 3-5 French sheath via the femoral artery, the tip of a pigtail catheter was advanced into the aorta to the level of the carina. CTAo was performed with the injection of 90 mL of nonionic contrast medium at a 1:2 dilution (Iopamiron 300; Bayer Yakuhin, Osaka, Japan) at a rate of 9 mL/s. CT images were obtained 8 s after the initiation of contrast medium injection, from the diaphragm to the kidney at 120 kVp with automatic tube current modulation, 0.838 pitch, 0.5 s per rotation, and a 64 × 0.5 mm data acquisition system. After data acquisition, axial images were reconstructed with a slice thickness of 1.0 mm and a slice interval of 0.5 mm. An experienced radiologic technologist identified target feeding arteries based on the axial CT images obtained by CTAo, and produced 3-dimensional (3D) vascular images using

a workstation (Synapse Vincent; Fujifilm Medical, Tokyo, Japan). A 3D vascular image was constructed based on our previous report [8].

Identification of EHFAs of HCC

Prior to TACE, CTAo was performed to obtain a detailed understanding of the vascular anatomy and to detect EHFAs. Subsequently, to allow for accurate evaluation of the spread of HCC in the liver and the vasculature, all patients underwent a baseline examination with DSA from the common or proper hepatic artery, CT during arterial portography, and CT during hepatic arteriography (CTHA) [10-12].

After the baseline examinations, CTAo images were compared with CTHA images. Areas of the target tumor showing enhancement on CTAo but not on CTHA indicated the existence of EHFAs. In these cases, we carefully analyzed the CTAo images, especially the arteries near the target tumor, to identify EHFAs. The EHFAs were color coded on the 3D vascular images to clearly identify them for the operator.

Statistical analysis

The SPSS software package, version 15.0 (SPSS Inc, Chicago, IL, USA), was used for statistical analysis. Continuous variables were expressed as medians (range) except for

the number of prior TACE treatments, which was expressed as a mean (range). Categorical variables were expressed as numbers (percentages). Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the chi-square test to assess the presence of EHFAs based on univariable analysis. Logistic regression analysis was used to estimate the odds ratio in the presence of EHFAs with the following parameters in all patients: AFP (≤ 20.0 ng/mL or > 20.0 ng/mL), AFP-L3 (≤ 10.0 % or > 10.0 %), DCP (≤ 40 mAU/ml or > 40 mAU/ml), tumor size (< 30 mm or ≥ 30 mm), tumor location in liver (surface or not surface), portal thrombus (absent or present), and the number of prior TACE treatments (< 3 or ≥ 3). We defined the tumor location as "surface" if at least one tumor was situated in the liver periphery. Logistic regression analysis was used to estimate the odds ratio in the presence of EHFAs with the following parameters among the subgroup of patients with HCC located on the liver surface (n=133): AFP (≤ 20.0 ng/mL or > 20.0 ng/mL), DCP (≤ 40 mAU/ml or > 40 mAU/ml), tumor size (< 30 mm or ≥ 30 mm) and the number of prior TACE treatments (< 3 or ≥ 3). We used the lower or upper limit of the reference values at our institution as cut-off values for laboratory data, as appropriate, and determined the cut-off values for the tumor number and number of TACE treatments undergone based on the analysis of receiver operating characteristic

curves (ROCs) (data not shown). Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

The clinical backgrounds of the study patients are shown in Table 1. The median age was 73 years, and there was a predominance of men (70.5%). One hundred forty-six patients had hepatitis related to hepatitis B or C virus (84.4%). With regard to liver function as categorized by Child-Pugh class, 116 (66.5%) patients were class A, 54 (31.8%) were class B, and 3 (1.7%) were class C. Regarding tumor factors, the median tumor size was 22 mm. There were 120 (69.2%) patients with multiple tumors and 11 (6.4%) with portal thrombi. Eighty-six of 173 patients (49.7%) had previously undergone TACE, and the mean number of prior TACE treatments was one (0-10).

Frequency and types of EHFAs of HCC patients.

Twenty-two patients with HCC had EHFAs (12.7%). Table 2 shows the types of EHFAs; the majority involved the right inferior phrenic artery (RIPA) (n=19). However, in one case the EHFA was an unknown artery supplied directly by the aorta (Fig. 1). Seventeen patients had undergone several previous TACE treatments for HCC. In the

remaining 5 patients with no history of TACE (RIPA only, n=4; RIPA and right adrenal artery, n=1), tumors were very large (median 109 mm, range 39-120), and 2 cases had ruptured tumors fed by the hepatic artery and inferior phrenic artery (IPA).

Factors associated with the presence of EHFAs in the entire patient population

Factors associated with the presence of EHFAs by univariate analysis were listed in Table 3. The following associations were statistically significant: AFP, AFP-L3, DCP, tumor size, tumor location in the liver, portal thrombus, history of TACE, and the number of prior TACE treatments. Of these, the factors that were significantly associated with the presence of EHFAs in multivariate analysis were tumor size ≥ 30 mm (hazard ratio (HR), 5.233 [95% confidence interval (CI), 1.507–17.413]; p = 0.009) and number of prior TACE treatments ≥ 3 (HR, 6.847 [95% CI, 1.928–24.311]; p = 0.003) (Table 4).

Factors associated with the presence of EHFAs among patients with HCC located on the liver surface

We subsequently investigated the subgroup of patients with HCC located on the liver surface, because the majority of patients (n=133, 76.9%) had at least one HCC located

on the liver surface in the present study. In this group, univariate analysis showed that the presence of EHFAs was significantly associated with the following factors: AFP, DCP, tumor size, history of TACE and number of prior TACE treatments. Of these, multivariate analysis identified the following as significant: tumor size ≥ 30 mm (HR, 6.259 [95% CI, 1.956–20.026]; p = 0.002) and number of prior TACE treatments ≥ 3 (HR, 10.345 [95% CI, 3.010–35.557]; p < 0.001) (Supplemental Tables 1 and 2).

Discussion

Previous studies noted the effectiveness of TACE with angio-CT, a technique that combines an angiographic imager with CT [13, 14]. Angio-CT is a useful modality for investigating hemodynamics and the process of differentiation from early to advanced HCC [15]. It has also improved the efficacy of TACE, prolonging survival rates in HCC patients [16]. In addition, CTAo images using the angio-MDCT system have enabled the rapid and accurate identification and subsequent catheterization of feeding arteries of HCC [8, 17]. In the present study, we assessed the frequencies and types of EHFAs in HCC patients based on CTAo images derived using the angio-CT system.

It is known that various types of EHFAs develop and supply HCC tumors. Previous reports have identified the inferior phrenic, internal mammary, gastric, cystic and

omental arteries as EHFAs supplying HCC [7, 18]. In this study, 12.7% of patients had EHFAs. Most involved the IPA, which has previously been identified as the most common source of EHFAs in patients with HCC [6, 19]. In one patient the EHFA was an unknown artery that branched directly from the aorta.

The conventional method of identifying EHFAs requires first expecting feeders based on DSA and CT imaging, then selecting each suspected artery and confirming whether it is an EHFA using DSA or contrast-enhanced CT. However, this method is time-consuming and may increase exposure to X-rays and contrast medium.

In contrast, CTAo using angio-MDCT can comprehensively scan and analyze a large area in a very short period of time. It reduces the physical and mental stress of operators and is more sensitive than the conventional method, making it possible to easily detect rare arteries like the unknown artery identified in the present study.

Arteries in CTAo images have high contrast compared with intra-venous CT angiography. In patients who underwent TACE or dynamic CT examination at our institution, images of the aorta derived by CTAo demonstrated double the CT number of those obtained with intra-venous CT angiography, thus increasing noise tolerance, and CTAo required a smaller volume of contrast medium (data not shown). Furthermore, CTAo is expected to be able to detect minute vessels that cannot be identified via

intra-venous CT angiography.

When we used multivariate analysis to determine the factors associated with the presence of EHFAs, tumor size ≥ 30 mm and number of prior TACE treatments ≥ 3 were selected as independent risk factors. Feeders of large HCCs tend to be extrahepatic arteries [20], and the presence of EHFAs should be a particular concern in such cases even if TACE is being performed for the first time (Fig. 2). On the other hand, repeated TACE induces hepatic arterial damage and increases the occurrence of EHFAs [6, 21]. The TACE procedure requires that the patient have satisfactory liver function. The percentage of HCC patients with Child-Pugh class A liver function is increasing in Japan because of treatment of viral hepatitis and the development of surveillance systems for HCC [22]. For these reasons, the number of HCC patients with good remnant liver function is expected to rise in the near future, and the opportunity for repeat TACE procedures will increase. Hence, it is important to be familiar with EHFAs of HCC and the appropriate TACE techniques to use in their presence.

Previous studies have reported a relationship between the presence of EHFAs and the location of HCC [6, 23]. In the present study, however, tumor location was a significant risk factor by univariable but not multivariable analysis. We therefore assessed the subgroup of patients with HCC located on the liver surface. Tumor size and number of

prior TACE treatments were identified as significant risk factors by logistic regression analysis, as was the case in the entire patient population. Close attention should be paid to the possible presence of EHFAs in advanced HCC patients with a history of repeat TACE, regardless of tumor location.

In the present study there were limitations in the examination of EHFAs by CTAo. Because CTAo was performed using contrast administered at the aorta, our assessment of the internal thoracic artery was limited. Although one patient had an EHFA involving the internal thoracic artery, we identified this artery via axial CT imaging.

In conclusion, repeat TACE procedures and tumor size were independent risk factors for the presence of EHFAs. The IPA was the most common EHFA, and therefore attention should be paid to this artery in patients with a history of repeat TACE procedures or large tumors. CTAo using angio-MDCT is very useful for rapid identification of other EHFAs, including unknown arteries. The use of CTAo images to locate EHFAs of HCC could provide accurate information on these unusual feeders of HCC, including their most common sources and any associated risk factors. Further prospective studies will be needed to assess whether TACE with CTAo using angio-MDCT contributes to prolonging survival rates in patients with HCC.

Reference

[1] Umemura T, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. Japanese Journal of Gastroenterology. 44 (2009) 102-107.

[2] The Japan Society of Hepatology (2013) Clinical Practice Guidelines for Hepatocellular Carcinoma 2013. Available via http://www.jsh.or.jp/English/guidelines_en/Guidelines_for_hepatocellular_carcinoma_2013. Accessed 4 Dec 2015.

[3] Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification, Semin Liver Dis. 19 (1999) 329-338.

[4] Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials, Radiology 224 (2002) 47-54.

[5] Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35 (2002) 1164-1171.

[6] Miyayama S, Matsui O, Taki K, et al. Extrahepatic blood supply to hepatocellular

carcinoma: angiographic demonstration and transcatheter arterial chemoembolization. Cardiovasc Intervent Radiol. 29 (2006) 39-48.

[7] Kim HC, Chung JW, Lee W, et al. Recognizing extrahepatic collateral vessels that supply hepatocellular carcinoma to avoid complications of transcatheter arterial chemoembolization. Radiographics 25 (2005) S25-S39.

[8] Takada K, Toyoda H, Kumada T, et al**.** Accurate and rapid identification of feeding arteries with multidetector-row angiography-assisted computed tomography for transarterial chemoembolization for hepatocellular carcinoma. Japanese Journal of Gastroenterology 50 (2015) 1190-1196.

[9] European Association for The Study of The Liver, European Organization for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 56 (2992) 908-943.

[10] Matsui O, Takashima T, Kadoya M, et al. Dynamic computed tomography during arterial portography: the most sensitive examination for small hepatocellular carcinomas. J Comput Assist Tomogr. 9 (1985) 19–24.

[11] Matsui O, Kadoya M, Suzuki M, et al. Work in progress: dynamic sequential computed tomography during arterial portography in the detection of hepatic neoplasms. Radiology 146 (1983) 721–727.

[12] Hayashi M, Matsui O, Ueda K, et al. Progression to hypervascular hepatocellular carcinoma: correlation with intranodular blood supply evaluated with CT during intraarterial injection of contrast material. Radiology 225 (2002) 143–149.

[13] Inaba Y, Arai Y, Kanematsu M, et al. Revealing hepatic metastases from colorectal cancer: value of combined helical CT during arterial portography and CT hepatic arteriography with a unified CT and angiography system. Am J Roentogenol. 174 (2000) 955–961.

[14] Takayasu K, Muramatsu Y, Maeda T, et al. Targeted transarterial oily chemoembolization for small foci of hepatocellular carcinoma using a unified helical CT and angiography system: analysis of factors affecting local recurrence and survival rates. AJR Am J Roentogenol. 176 (2001) 681–688.

[15] Kitao A, Zen Y, Matsui O, Gabata T, Nakanuma Y, Hepatocarcinogenesis: multistep changes of drainage vessels at CT during arterial portography and hepatic arteriography—radiologic– pathologic correlation. Radiology 252 (2009) 605–614.

[16] Toyoda H, Kumada T, Sone Y, Impact of a unified CT angiography system on outcome of patients with hepatocellular carcinoma. AJR Am J Roentogenol. 192 (2009) 766–774.

[17] Minamiguchi H, Kawai N, Sato M, et al. Hepatoma feeding arteriogram created by CT during aortography using IVR 64-multidetector-row CT for catheterization in transcatheter arterial chemoembolization for hepatocellular carcinoma. Jpn J Radiol. 31 (2013) 428–436.

[18] Takeuchi Y, Arai Y, Inaba Y, Ohno K, Maeda T, Itai Y. Extrahepatic arterial supply to the liver: observation with a unified CT and angiography system during temporary balloon occlusion of the proper hepatic artery. Radiology 209 (1998) 121-128.

[19] Sueyoshi E, Hayashida T, Sakamoto I, Uetani M. Vascular complications of hepatic artery after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. Am J Roentgenol. 195 (2010) 245-251.

[20] Park SI, Lee DY, Won JY, Lee JT. Extrahepatic collateral supply of hepatocellular carcinoma by the intercostal arteries. J Vasc Interv Radiol. 14 (2003) 461-468.

[21] Nakai M, Sato M, Kawai N, et al. Hepatocellular carcinoma: Involvement of the internal mammary artery. Radiology 219 (2001) 147–152.

[22] Toyoda H, Kumada T, Tada T, Sone Y, Kaneoka Y, Maeda A. Characteristics and prognosis of patients with hepatocellular carcinoma after the year 2000 in Japan. J Gastroenterol Hepatol 26 (2011) 1765–1771.

[23] Chen GW, Song B, Li ZL, Yuan Y. Ectopic blood supply of hepatocellular carcinoma as depicted by angiography with computed tomography: associations with morphological features and therapeutic history. PLoS One. 8 (2013) e71942.

Table

Table 1. Clinical backgrounds of study patients (n=173).

Age (years)	73 (37–88)
Sex (female / male)	51 (29.5%) / 122 (70.5%)
Etiology (HBV / HCV / non-HBV and non-HCV)	21 (12.1%) / 125 (72.3%) / 27 (15.6%)
Alcohol abuse (negative / positive) *	161 (93.1%) / 12 (6.9%)
Child-Pugh classification (A / B / C)	116 (66.5%) / 54 (31.8%) / 3 (1.7%)
AFP (ng/mL)	16.9 (0.3–106851)
AFP-L3 (%)	6.0 (0–99.5)
DCP (mAU/mL)	57 (5–50000)
Tumor size (mm)	22 (7–120)
Tumor number (single / multiple)	53 (30.8%) / 120 (69.2%)
Portal thrombus (absent / present)	162 (93.6%) / 11 (6.4%)
Primary / Recurrence	35 (20.2%) / 138 (79.8%)
Initial treatment (n=138)	
Hepatectomy / LAT** / TACE / HAIC	52 (37.7%) / 47 (34.1%) / 36 (26.1%) / 3 (2.1%)
Replace (+ / −)	29 (16.8%) / 144 (83.2%)
History of TACE (+ / −)	86 (49.7%) / 87 (50.3%)
Number of prior TACE treatments †	1 (0–10)

Values are expressed as medians (range) except for the number of prior TACE treatments (†mean (range))

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive α-fetoprotein; DCP, des-γ-carboxy prothrombin; LAT, locoregional ablative therapy; TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

* Alcohol abuse was defined as intake ≥ 60 g/day.

** LAT included radiofrequency ablation and ethanol injection.

Table 2. Types of extra-hepatic feeding arteries in hepatocellular carcinoma patients. (n=22)

	Number
RIPA only	16
RIPA + RARA	1
RIPA + branch of SMA	1
RIPA + RRA + RITA	1
RRA	1
RARA	1
unknown artery (from aorta)	1

RIPA, right inferior phrenic artery; RARA, right adrenal artery; SMA, superior mesenteric artery; RRA, right renal artery; RITA, right internal thoracic artery.

Table 3. Factors associated with the presence of extra-hepatic feeding arteries based on univariable analysis.

Factor	EHFA absent (n=151)	EHFA present (n=22)	p value
Age (years)	73 (37–88)	72 (42–85)	0.834
Sex (female / male)	45 (29.8%) / 106 (70.2%)	6 (27.3%) / 16 (72.7%)	0.808
Etiology (HBV / HCV / non-HBV and non-HCV)	17 (11.3%) / 108 (71.5%) / 26 (17.2%)	4 (18.2%) / 17 (77.3%) / 1 (4.5%)	0.244
Alcohol abuse (negative / positive) *	139 (92.1%) / 12 (7.9%)	0 (0%) / 22 (100%)	0.171
Child-Pugh classification (A / B / C)	102 (67.5%) / 46 (30.5%) / 3 (2.0%)	14 (63.6%) / 8 (36.4%) / 0 (0%)	0.706
AFP (ng/mL)	14.6 (0.3–106851)	177.6 (6.1–19932.7)	< 0.001
AFP-L3 (%)	5.4 (0–99.5)	7.4 (0.5–84.7)	0.029
DCP (mAU/mL)	44 (5–50000)	294.5 (15–50000)	< 0.001
Tumor size (mm)	21 (8–108)	35 (7–120)	< 0.001
Tumor number (single / multiple)	48 (31.8%) / 103 (68.2%)	5 (22.7%) / 17 (77.3%)	0.389
Portal thrombus (absent / present)	144 (95.4%) / 7 (4.6%)	4 (18.2%) / 18 (81.8%)	0.015
Tumor location in liver (surface / not surface)	112 (74.2%) / 39 (25.8%)	21 (95.5%) / 1 (4.5%)	0.027
Replace (+ / −)	25 (16.6%) / 126 (83.4%)	4 (18.2%) / 18 (81.8%)	0.849
History of TACE (+ / −)	69 (45.7%) / 82 (54.3%)	17 (77.3%) / 5 (22.7%)	0.006
Number of prior TACE treatments †	1 (0–9)	3 (0–10)	< 0.001

Values are expressed as medians (range) except for the number of prior TACE treatments. † mean(range).

EHFA, extra-hepatic feeding arteries; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive α-fetoprotein; DCP, des-γ-carboxy prothrombin; TACE, transcatheter arterial chemoembolization

* Alcohol abuse was defined as intake ≥ 60 g/day.

Table 4. Factors associated with the presence of extra-hepatic feeding arteries based on multivariable analysis (logistic regression analysis).

Factor		**Odds ratio**	**95% CI**	**p value**
Tumor size (mm)	< 30	1		
	≥ 30	5.233	1.507–17.413	0.009
Number of prior TACE treatments	< 3	1		
	≥ 3	6.847	1.928–24.311	0.003

CI, confidence interval;

TACE, transcatheter arterial chemoembolization

Figure caption

Figure 1

A case of hepatocellular carcinoma partly fed by an extrahepatic artery from the aorta

80-years-old woman with hepatocellular carcinoma (HCC) partly supplied by an extrahepatic artery from the aorta. The confluent multinodular-type HCC is depicted as an enhancement on computed tomography (CT) aortography (a, *red circle*). CT during hepatic arteriography shows that only the periphery of this tumor was supplied by the proper hepatic artery (b, *yellow arrow*). The other parts of this tumor were supplied by the extrahepatic artery (c, enhanced CT via the feeder directly branching from the aorta; d, 3D vascular image). We performed digital subtraction angiography and selective transcatheter arterial chemoembolization for this HCC via the identified artery (e).

Figure2

A case of large hepatocellular carcinoma fed by the posterior branch of the right hepatic artery and the right inferior phrenic artery.

79-years-old woman with a large hepatocellular carcinoma (HCC) fed by the posterior branch of the right hepatic artery and the right inferior phrenic artery (RIPA). This patient had no history of transcatheter arterial chemoembolization. This massive HCC enhanced heterogeneously on computed tomography (CT) aortography (a). The tumor enhanced on CT during hepatic arteriography (b), however the enhancement was poor compared with CT aortography. With a 3D vascular image constructed from CT aortography images, we were able to identify the RIPA as the extrahepatic feeding artery (c). The feeders to the HCC from the hepatic artery and the RIPA were confirmed by digital subtraction angiography at the celiac artery (d).

Table(s)

Table 1. Clinical backgrounds of study patients (n=173).

Age (years)	73 (37–88)
Sex (female / male)	51 (29.5%) / 122 (70.5%)
Etiology (HBV / HCV / non-HBV and non-HCV)	21 (12.1%) / 125 (72.3%) / 27 (15.6%)
Alcohol abuse (negative / positive) *	161 (93.1%) / 12 (6.9%)
Child-Pugh classification (A / B / C)	116 (66.5%) / 54 (31.8%) / 3 (1.7%)
AFP (ng/mL)	16.9 (0.3–106851)
AFP-L3 (%)	6.0 (0–99.5)
DCP (mAU/mL)	57 (5–50000)
Tumor size (mm)	22 (7–120)
Tumor number (single / multiple)	53 (30.8%) / 120 (69.2%)
Portal thrombus (absent / present)	162 (93.6%) / 11 (6.4%)
Primary / Recurrence	35 (20.2%) / 138 (79.8%)
Initial treatment (n=138)	
Hepatectomy / LAT** / TACE / HAIC	52 (37.7%) / 47 (34.1%) / 36 (26.1%) / 3 (2.1%)
Replace (+ / −)	29 (16.8%) / 144 (83.2%)
History of TACE (+ / −)	86 (49.7%) / 87 (50.3%)
Number of prior TACE treatments †	1 (0–10)

Values are expressed as medians (range) except for the number of prior TACE treatments (†mean (range))

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive α-fetoprotein; DCP, des-γ-carboxy prothrombin; LAT, locoregional ablative therapy; TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

* Alcohol abuse was defined as intake ≥ 60 g/day.

** LAT included radiofrequency ablation and ethanol injection.

Table 2. Types of extra-hepatic feeding arteries in hepatocellular carcinoma patients. (n=22)

	Number
RIPA only	16
RIPA + RARA	1
RIPA + branch of SMA	1
RIPA + RRA + RITA	1
RRA	1
RARA	1
unknown artery (from aorta)	1

RIPA, right inferior phrenic artery; RARA, right adrenal artery; SMA, superior mesenteric artery; RRA, right renal artery; RITA, right internal thoracic artery.

Table 3. Factors associated with the presence of extra-hepatic feeding arteries based on univariable analysis.

Factor	EHFA absent (n=151)	EHFA present (n=22)	p value
Age (years)	73 (37–88)	72 (42–85)	0.834
Sex (female / male)	45 (29.8%) / 106 (70.2%)	6 (27.3%) / 16 (72.7%)	0.808
Etiology (HBV / HCV / non-HBV and non-HCV)	17 (11.3%) / 108 (71.5%) / 26 (17.2%)	4 (18.2%) / 17 (77.3%) / 1 (4.5%)	0.244
Alcohol abuse (negative / positive) *	139 (92.1%) / 12 (7.9%)	0 (0%) / 22 (100%)	0.171
Child-Pugh classification (A / B / C)	102 (67.5%) / 46 (30.5%) / 3 (2.0%)	14 (63.6%) / 8 (36.4%) / 0 (0%)	0.706
AFP (ng/mL)	14.6 (0.3–106851)	177.6 (6.1–19932.7)	< 0.001
AFP-L3 (%)	5.4 (0–99.5)	7.4 (0.5–84.7)	0.029
DCP (mAU/mL)	44 (5–50000)	294.5 (15–50000)	< 0.001
Tumor size (mm)	21 (8–108)	35 (7–120)	< 0.001
Tumor number (single / multiple)	48 (31.8%) / 103 (68.2%)	5 (22.7%) / 17 (77.3%)	0.389
Portal thrombus (absent / present)	144 (95.4%) / 7 (4.6%)	4 (18.2%) / 18 (81.8%)	0.015
Tumor location in liver (surface / not surface)	112 (74.2%) / 39 (25.8%)	21 (95.5%) / 1 (4.5%)	0.027
Replace (+ / −)	25 (16.6%) / 126 (83.4%)	4 (18.2%) / 18 (81.8%)	0.849
History of TACE (+ / −)	69 (45.7%) / 82 (54.3%)	17 (77.3%) / 5 (22.7%)	0.006
Number of prior TACE treatments †	1 (0–9)	3 (0–10)	< 0.001

Values are expressed as medians (range) except for the number of prior TACE treatments. † mean(range).

EHFA, extra-hepatic feeding arteries; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive α-fetoprotein; DCP, des-γ-carboxy prothrombin; TACE, transcatheter arterial chemoembolization

* Alcohol abuse was defined as intake ≥ 60 g/day.

Table 4. Factors associated with the presence of extra-hepatic feeding arteries based on multivariable analysis (logistic regression analysis).

Factor		**Odds ratio**	**95% CI**	**p value**
Tumor size (mm)	< 30	1		
	≥ 30	5.233	1.507–17.413	0.009
Number of prior TACE treatments	< 3	1		
	≥ 3	6.847	1.928–24.311	0.003

CI, confidence interval;

TACE, transcatheter arterial chemoembolization

Figure 1a

Click here to download high resolution image

Figure 1b

Click here to download high resolution image

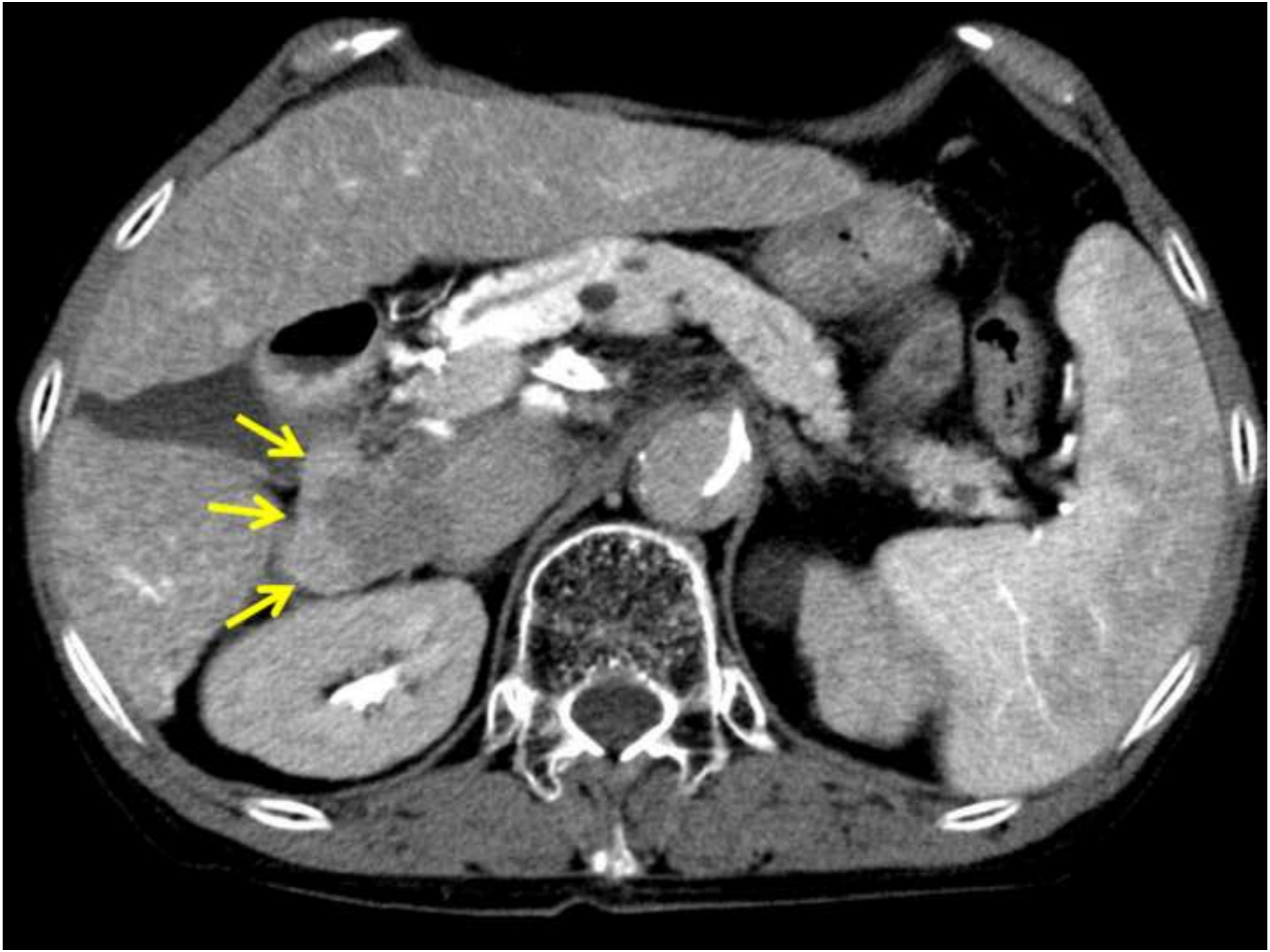

Figure 1c

Click here to download high resolution image

Figure 1d

Click here to download high resolution image

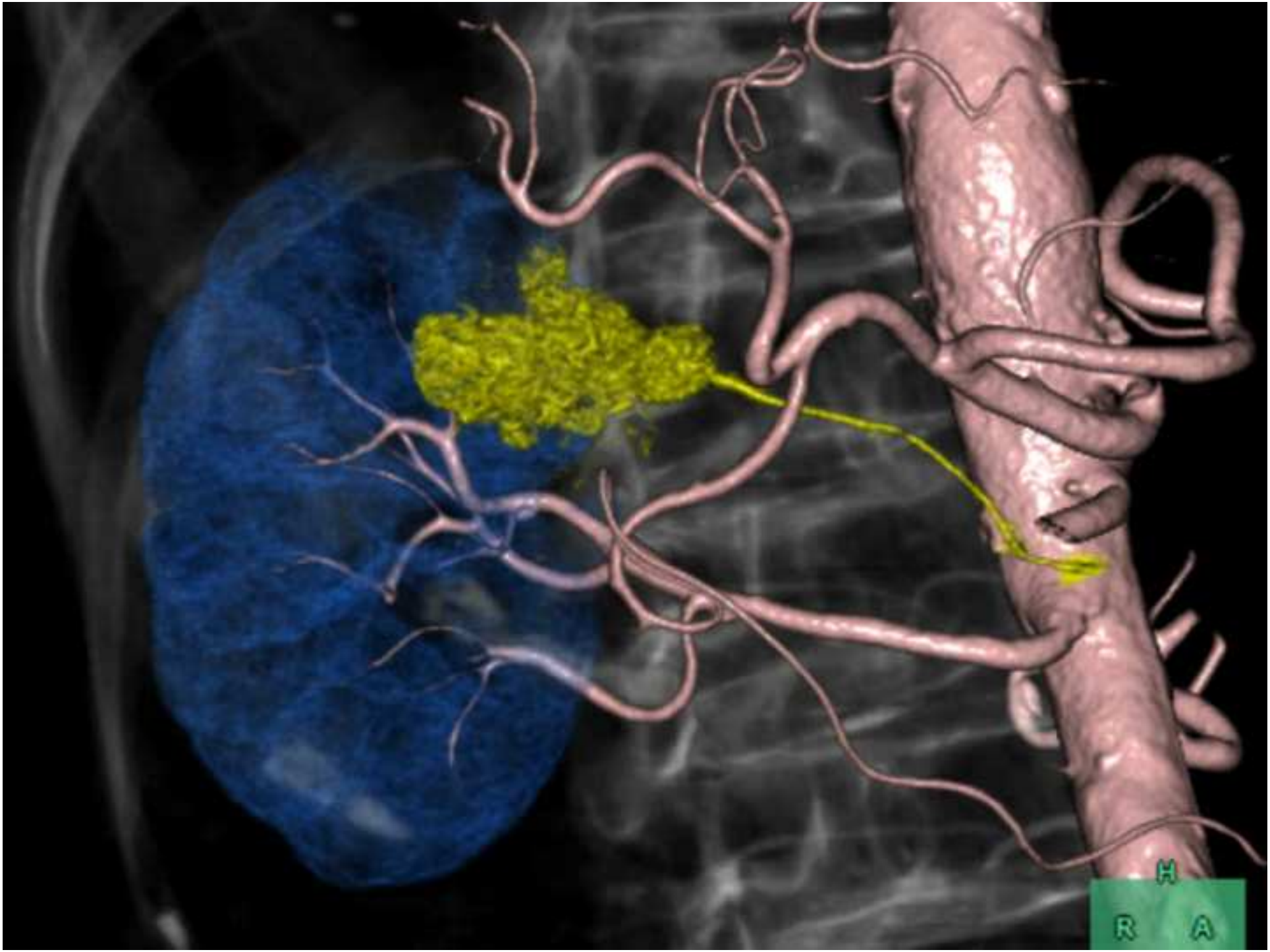

Figure 1e

Click here to download high resolution image

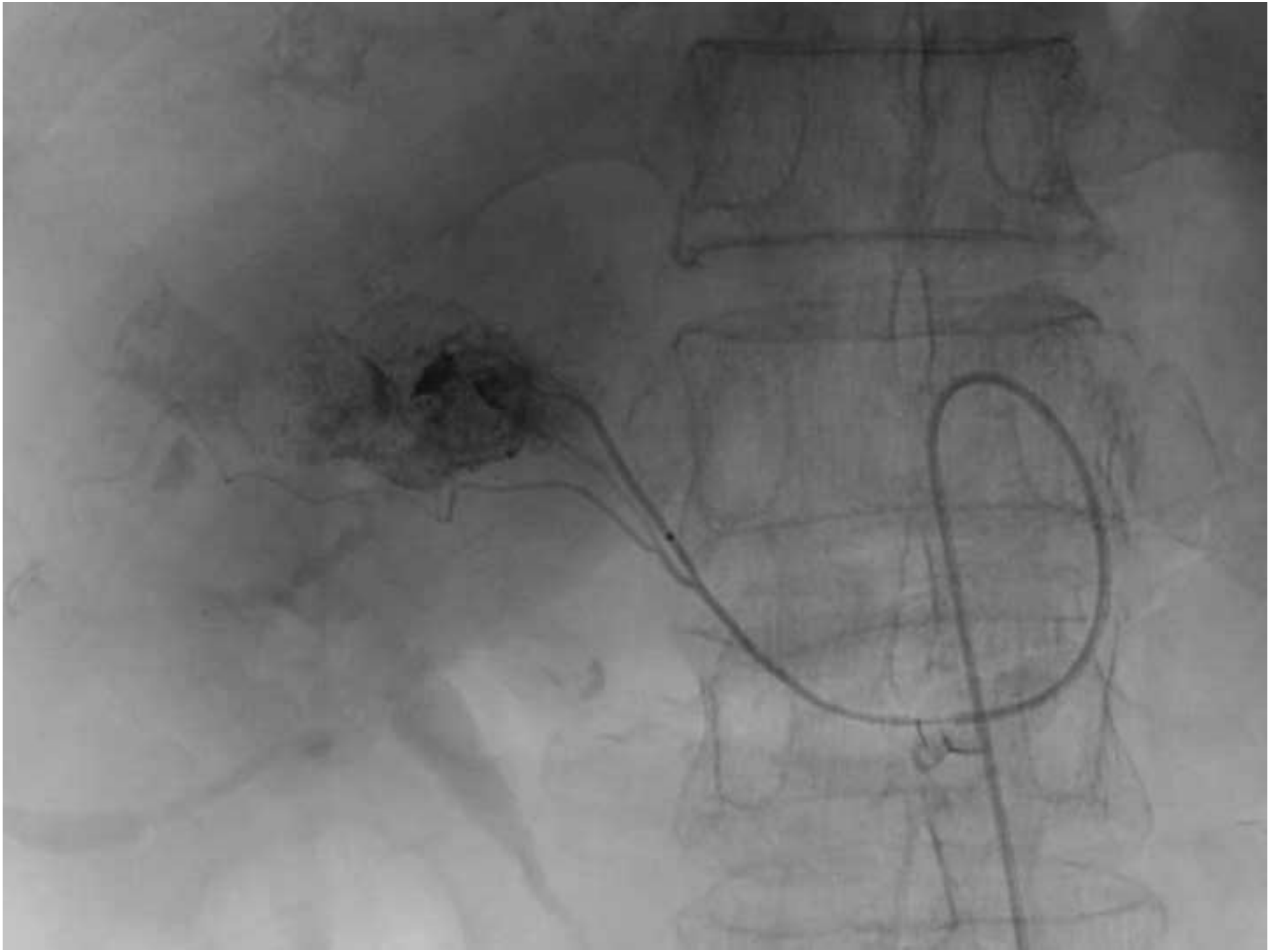

Figure 2a

Click here to download high resolution image

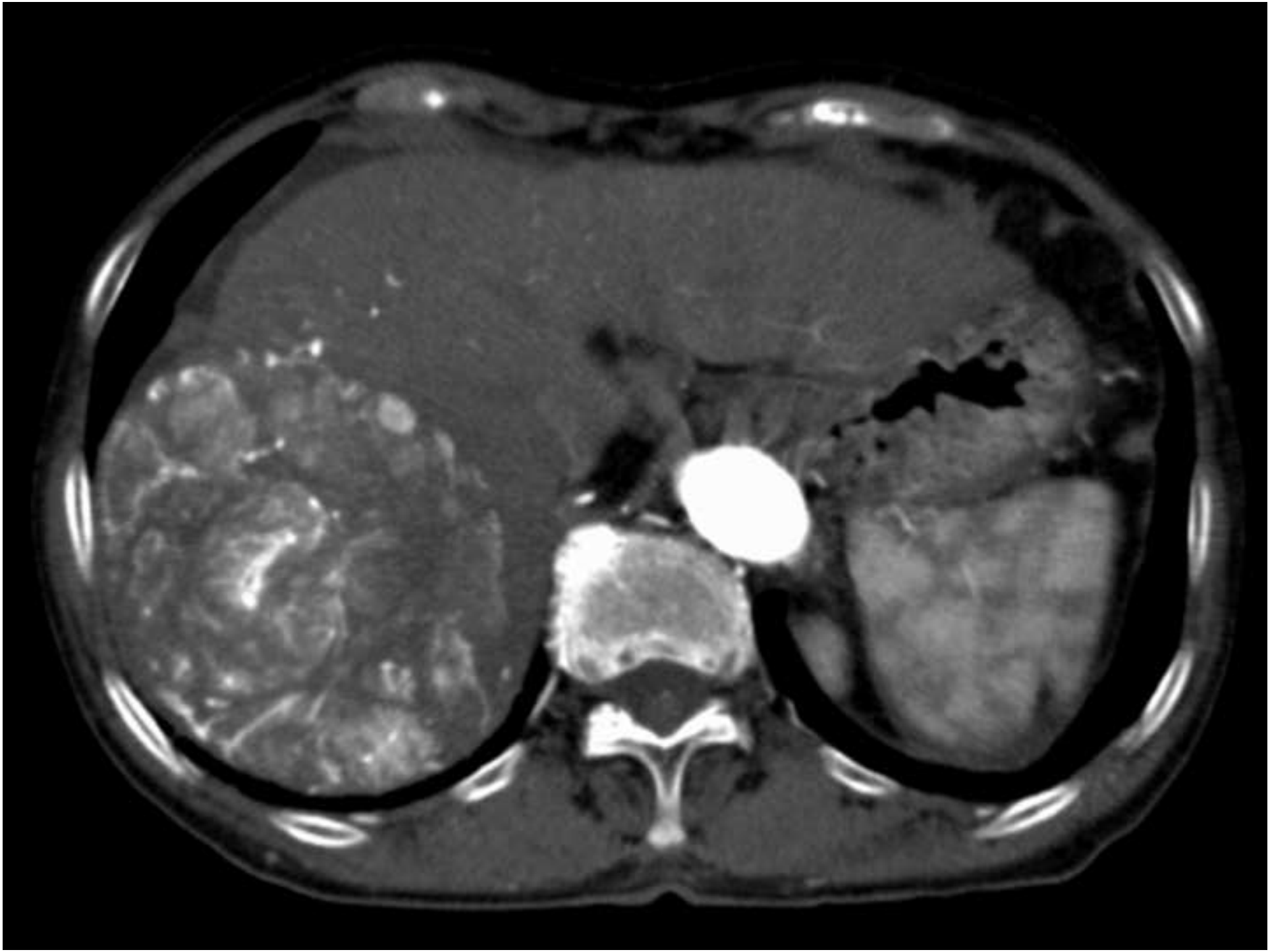

Figure 2b

Click here to download high resolution image

Figure 2c

Click here to download high resolution image

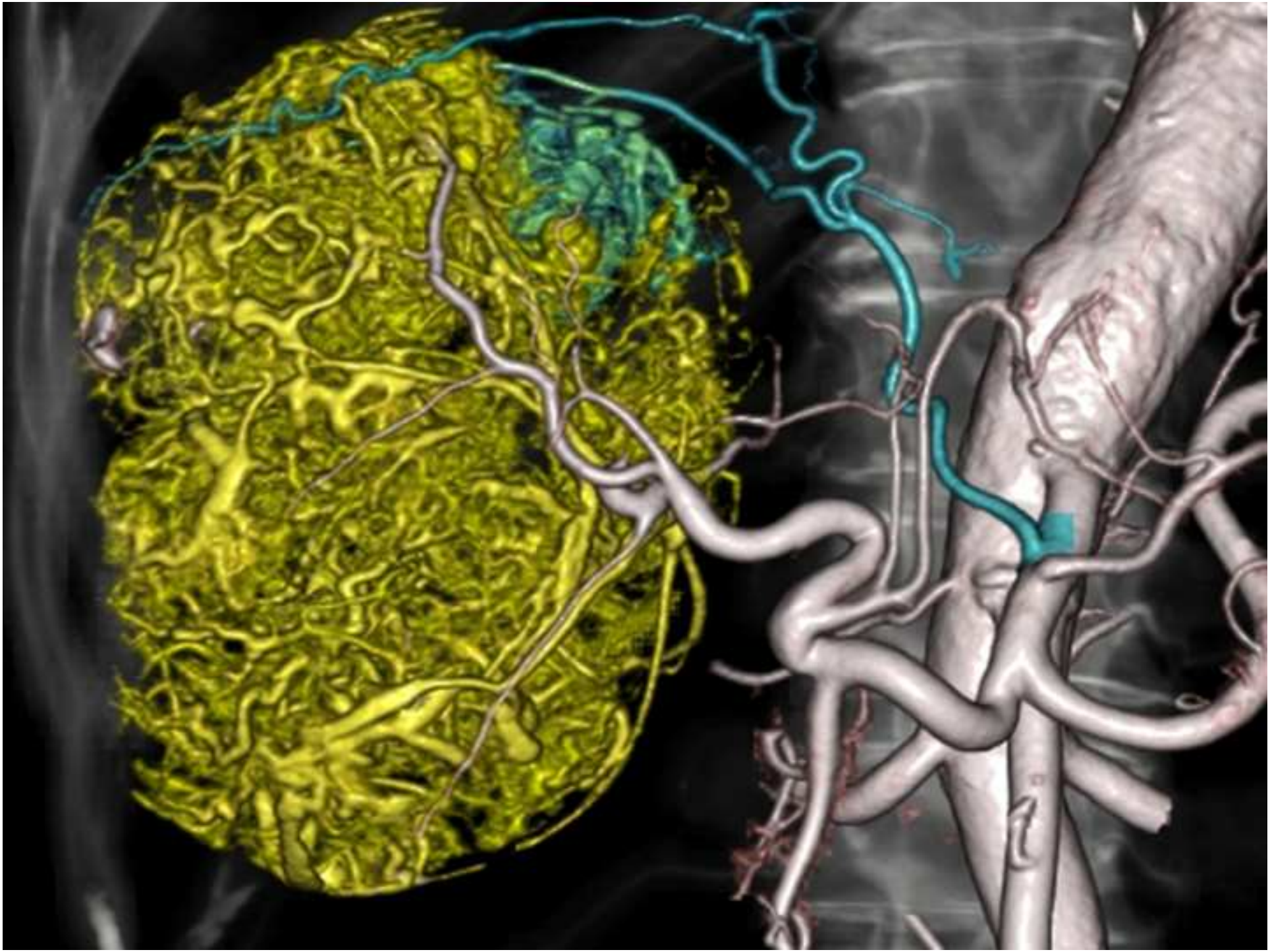

Figure 2d

Click here to download high resolution image